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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/926,154	12/26/2001	Toshiaki Tagawa	P21462	2932

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/926,154	TAGAWA ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-15 and 17-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15 and 17-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment entered May 28, 2004 is acknowledged and has been entered.

Specification

1. The disclosure is objected to because of the following informalities: On page 1, next to last line of the page the disclosure "abs nt" should be --absent--.

On page 5, next to last line of page 5 the disclosure "us d" should be --used--.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1, 2, 4-15 and 17-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, line 3 the recitation "can be" is vague and indefinite. The recitation is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. Is the free target recognized by the ligands at equivalent level as the non-free target when not bound to the microparticle or not?

Claim 2 is vague and indefinite because it is unclear if the two ligands bound to the microparticles further comprise ligands having the same binding affinity (if so please direct Examiner's attention to support in the specification) or do the two ligands bound to the microparticles have the same binding affinity?

Claim 27 is vague and indefinite because it is unclear if the two ligands further comprises two more ligands of a same kind or if applicant intends that the two ligands bound to the microparticle are the same ligand.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 2, 5, 7-14, 17, 19-22 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Hosokawa et al (EP 0520499).

Hosokawa et al disclose liposomes (microparticle) bonded to human monoclonal antibodies (page 2, lines 1-4). Hosokawa et al disclose the antibody can be 1-3-1 to gastric cancer cell line MKN45 (non-free target). Hosokawa et al disclose that the liposome can contain an anti-cancer agent (page 2, line 4). Hosokawa et al disclose that the anti-cancer agent can be Adriamycin (p. 4, lines 26-27). Hosokawa et al disclose that the liposome may be reacted with polyalkylene glycol (water-soluble macromolecule) to modify the liposome surface. Hosokawa et al disclose the liposome can be modified by polyethylene glycol (page 12).

With respect to "the at least two ligands" as recited in the instant claims. One skilled in the art would recognize that the liposome of Hosokawa et al would comprise more than one of the antibodies on its surface. Therefore, Hosokawa et al teaches at least two ligands. Further, since there would be more than one antibody on the surface

of the liposome (same as recited in the instant claims). The liposome of Hosokawa would posses increased affinity to the non-free target.

With respect to "the ligand having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when not bound to the microparticle" as recited in the instant claims. Since Hosokawa et al teaches that the ligand can be a human monoclonal 1-3-1 antibody directed to MKN 45 (human gastric cancer cell) (same type of antibody that applicant discloses on page 4, lines 21 and 22, a human cancer cell-reactive monoclonal antibody). The ligand of the liposome of Hosokawa et al would posses the property of having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when no bound to the microparticle.

Further, since Hosokawa teaches the same type of 1-3-1 antibody (human cancer cell-reactive human monoclonal antibody) directed to the same antigen (MKN 45), Hosokawa et al disclose the ligand-bonded complex as claimed and therefore, it would comprise the increasing affinity of the dissociation constant as recited in the instant claims.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 2, 5, 7-14, 17, 19-22 and 24-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Hosokawa et al (US 5,767,246).

Hosokawa et al disclose liposomes (microparticle) bonded to human monoclonal antibodies (col 1, lines 1-12). Hosokawa et al disclose the antibody can be 1-3-1 antibody that binds to gastric cancer cell line MKN45 (non-free target). Hosokawa et al disclose that the liposome can contain an anti-cancer agent (col 1, line 14). Hosokawa et al disclose that the anti-cancer agent can be adriamycin (col 4, lines 53-56). Hosokawa et al disclose that the liposome may be reacted with polyalkylene glycol (water-soluble macromolecule) to modify the liposome surface. Hosokawa et al disclose the liposome can be modified by polyethylene glycol (col 14).

With respect to "the at least two ligands" as recited in the instant claims. One skilled in the art would recognize that the liposome of Hosokawa et al would comprise more than one of the antibodies on its surface. Therefore, Hosokawa et al teaches at least two ligands. Further, since there would be more than one antibody on the surface of the liposome (same as recited in the instant claims). The liposome of Hosokawa would posses increased affinity to the non-free target.

With respect to "the ligand having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when not bound to the microparticle" as recited in the instant claims. Since Hosokawa et al teaches that the ligand can be a human monoclonal 1-3-1 antibody directed to MKN 45 (human gastric cancer cell) (same type of antibody that applicant discloses on page 4, lines 21 and 22, a human cancer cell-reactive monoclonal antibody). The ligand of the liposome of Hosokawa et al would posses the property of having affinity for both a free target and a non-free target so that the free

target can be recognized by the ligand at an equivalent level as the non-free target when no bound to the microparticle.

Further, since Hosokawa teaches the same type of 1-3-1 antibody (human cancer cell-reactive human monoclonal antibody) directed to the same antigen (MKN 45), Hosokawa et al disclose the ligand-bonded complex as claimed and therefore, it would comprise the increasing affinity of the dissociation constant as recited in the instant claims.

7. Claims 1, 2, 5, 7-14, 17-22 and 24-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Hosokawa et al (US 6,139,869).

Hosokawa et al disclose liposomes (microparticle) bonded to human monoclonal antibodies (col 1, lines 1-19). Hosokawa et al disclose the antibody can be 1-3-1 antibody that binds to gastric cancer cell line MKN45 (non-free target). Hosokawa et al disclose that the liposome can contain an anti-cancer agent (col 1, line 19). Hosokawa et al disclose that the anti-cancer agent can be adriamycin (col 5, lines 3-6). Hosokawa et al disclose that the liposome may be reacted with polyalkylene glycol (water-soluble macromolecule) to modify the liposome surface. Hosokawa et al disclose the liposome can be modified by polyethylene glycol (col 15-16). Hosokawa et al disclose that the liposome bound to the antibody is a pharmaceutical composition (col 16 and claim 1).

With respect to "the at least two ligands" as recited in the instant claims. One skilled in the art would recognize that the liposome of Hosokawa et al would comprise more than one of the antibodies on its surface. Therefore, Hosokawa et al teaches at least two ligands. Further, since there would be more than one antibody on the surface

of the liposome (same as recited in the instant claims). The liposome of Hosokawa would posses increased affinity to the non-free target.

With respect to "the ligand having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when not bound to the microparticle" as recited in the instant claims. Since Hosokawa et al teaches that the ligand can be a human monoclonal 1-3-1 antibody directed to MKN 45 (human gastric cancer cell) (same type of antibody that applicant discloses on page 4, lines 21 and 22, a human cancer cell-reactive monoclonal antibody). The ligand of the liposome of Hosokawa et al would posses the property of having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when no bound to the microparticle.

Further, since Hosokawa teaches the same type of 1-3-1 antibody (human cancer cell-reactive human monoclonal antibody) directed to the same antigen (MKN 45), Hosokawa et al disclose the ligand-bonded complex as claimed and therefore, it would comprise the increasing affinity of the dissociation constant as recited in the instant claims.

8. Claims 1, 2, 5, 7-14, 17-22 and 24-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Hosokawa (US 5,990,297) or Hosokawa et al (US 5990,287) or Hosokawa (US 5,837,845).

Hosokawa et al ('287, '297 & '845) disclose liposomes (microparticle) bonded to human monoclonal antibodies. Hosokawa et al disclose the antibody can be 1-3-1

antibody that binds to gastric cancer cell line MKN45 (non-free target). Hosokawa et al disclose that the liposome can contain an anti-cancer agent. Hosokawa et al disclose that the anti-cancer agent can be adriamycin . Hosokawa et al disclose that the liposome may be reacted with polyalkylene glycol (water-soluble macromolecule) to modify the liposome surface. Hosokawa et al disclose the liposome can be modified by polyethylene glycol.

With respect to "the at least two ligands" as recited in the instant claims. One skilled in the art would recognize that the liposome of Hosokawa et al ('287 & '297) would comprise more than one of the antibodies on its surface. Therefore, Hosokawa et al teaches at least two ligands. Further, since there would be more than one antibody on the surface of the liposome (same as recited in the instant claims). The liposome of Hosokawa would posses increased affinity to the non-free target.

With respect to "the ligand having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when not bound to the microparticle" as recited in the instant claims. Since Hosokawa et al ('287, '297 & '845)) teaches that the ligand can be a human monoclonal 1-3-1 antibody directed to MKN 45 (human gastric cancer cell) (same type of antibody that applicant discloses on page 4, lines 21 and 22, a human cancer cell-reactive monoclonal antibody). The ligand of the liposome of Hosokawa et al would posses the property of having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when no bound to the microparticle.

Further, since Hosokawa ('287, '297 & '845) teaches the same type of 1-3-1 antibody (human cancer cell-reactive human monoclonal antibody) directed to the same antigen (MKN 45), Hosokawa et al disclose the ligand-bonded complex as claimed and therefore, it would comprise the increasing affinity of the dissociation constant as recited in the instant claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1, 2, 5, 7-14, 17, 19-22 and 24-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagawa et al (Us 5,264,221) in view of Hosokawa et al (EP 5,767,246).

Tagawa et al disclose a liposome (microparticle) bonded to at least one antibody (ligand). Tagawa et al disclose that this antibody can be a human monoclonal antibody directed to MKN 45 (non-free target) (col 7 & 8). Tagawa et al disclose polyalkylene glycol (water-soluble macromolecule) bonded to the liposomes. Tagawa et al disclose polyethylene glycol (PEG)-modified liposomes (col 2, lines 1-40). Tagawa et al disclose the liposome can comprise adrimaycin (col 3).

Tagawa et al differ from the instant invention in failing to teach dissociation constant with the free target and non-free target of at least about E-8 (M).

Hosokawa et al disclose human monoclonal 1-3-1 antibodies having affinity for MKN45 cancer cells. Hosokawa et al disclose that these antibodies recognize these antigens dominantly expressed on the surface of cell membrane of cancer cells (col 12). Hosokawa et al also disclose that these antibodies are useful for diagnosis and therapy of cancer.

It would have been obvious to one or ordinary skill in the art to incorporate antibodies as taught by Hosokawa et al into the liposome of Tagawa et al because Tagawa et al is generic with respect to the human monoclonal antibody directed to MKN 45 and Hosokawa et al teaches that these antibodies recognize these antigens

dominantly expressed on the surface of cell membrane of cancer cells. Hosokawa et al also disclose that these antibodies are useful for diagnosis and therapy of cancer. Therefore, one of ordinary skill in the art to have a reasonable expectation of success using the antibodies of Hosokawa et al with the liposomes of Tagawa et al.

With respect to "the at least two ligands" as recited in the instant claims. One skilled in the art would recognize that the liposome of Tagawa et al would comprise more than one of the antibodies on its surface. Therefore, Tagawa et al teaches at least two ligands. Further, since there would be more than one antibody on the surface of the liposome (same as recited in the instant claims). The liposome of Tagawa would posses increased affinity to the non-free target.

With respect to "the ligand having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when not bound to the microparticle" as recited in the instant claims. Since Tagawa et al and Hosokawa et al teaches that the ligand can be a human monoclonal 1-3-1 antibody directed to MKN 45 (human gastric cancer cell) (same type of antibody that applicant discloses on page 4, lines 21 and 22, a human cancer cell-reactive monoclonal antibody). The ligand of the modified liposome of Tagawa et al would posses the property of having affinity for both a free target and a non-free target so that the free target can be recognized by the ligand at an equivalent level as the non-free target when no bound to the microparticle.

Further, since the combination of Tagawa et al and Hosokawa teaches the same type of antibody (human cancer cell-reactive human monoclonal antibody)

directed to the same antigen (MKN 45), Tagawa et al and Hosokawa et al disclose the ligand-bonded complex as claimed and therefore, it would comprise the increasing affinity of the dissociation constant as recited in the instant claims.

13. Claims 6, 15 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hosokawa et al (EP 052499) in view of Allen et al (US 5,527,528).

See above for teachings of Tagawa et al and Hosokawa et al.

Hosokawa et al differ from the instant invention if failing to specifically teach that the at least two ligands are indirectly bonded to the microparticle by polyethylene glycol.

Allen et al disclose liposomes containing an anti-tumor compound in liposome entrapped from. Allen et al disclose monoclonal antibodies coupled to the liposome by polyethylene glycol chains (col 2 & col 4, lines 17-67). Allen et al disclose that the coupling of antibodies to the peg molecule allows the antibody in the polymer layer to be positioned at a selected depth in the layer, as shown to increase or decrease the extent to which the antibody is buried in the polymer layer (col 4, lines 51-60). Allen et al also disclose that these peg-coupled antibodies provide liposomes with an extended blood circulation time to a site to obtain greater therapeutic activity of a liposome-entrapped compound (col 3).

It would have been obvious to one of ordinary skill in the art to couple antibodies to polyethylene glycol molecules as taught by Allen et al into the liposome of Hosokawa et al because Allen et al shows that the coupling of antibodies to the peg molecule allows the antibody in the polymer layer to be positioned at a selected depth in the layer, as shown to increase or decrease the extent to which the antibody is buried in the

polymer layer. Allen et al also shows that these peg-coupled antibodies provide liposomes with an extended blood circulation time to a site to obtain greater therapeutic activity of a liposome-entrapped compound (col 3).

14. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hosokawa (EP 0520499) et al in view of Lindhofer et al (US 6,294,167).

Hosokawa et al differ from the instant invention in failing to specifically teach the ligand-bonded complex in a pharmaceutical composition.

Lindhofer et al disclose immunoliposomes which have monoclonal antibodies bound on their surfaces. Lindhofer et al disclose that these immunoliposomes are contained in pharmaceutical compositions (col 6). Lindhofer et al disclose that these compositions provide for particular tumor cells, to be distinguished from other cells on account of the recognition of specific marker antigens and are therefore suitable for immunological cell therapy and the pharmaceutical compositions lend themselves to in vivo and in vitro therapy of different tumor types (col 1).

It would have been obvious to one of ordinary skill in the art to incorporate pharmaceutical compositions as taught by Lindhofer et al with the liposomes of Hosokawa et al because Lindhofer et al shows that these compositions provide for particular tumor cells, to be distinguished from other cells on account of the recognition of specific marker antigens and are therefore suitable for immunological cell therapy and the pharmaceutical compositions lend themselves to in vivo and in vitro therapy of different tumor types.

Response to Arguments

15. Applicant's arguments with respect to claims 1, 2, 4-15, 17-26 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary W. Counts
Examiner
Art Unit 1641
July 12, 2004

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07/23/04